IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of
CHANG et al.

Serial No: 10/126,790

Filed: April 19, 2002

For: COMBINATION OF BRIMONIDINE AND TIMOLOL FOR TOPICAL OPHTHALMIC USE

Group Art Unit: 1614

Examiner: Brian S. Kwon

Confirmation No. 3467

DECLARATION OF AN EXPERT REGARDING FACTS RELEVANT TO PATENTABILITY (37 C.F.R. § 1.132)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PURPOSE OF DECLARATION

1. This declaration is to establish evidence of patentability of one or more claims of the above referenced application.

2. The persons making this declaration is an expert in the relevant art.

TESTIMONY OF EXPERT RELEVANT TO PATENTABILITY

3. The table attached herewith, labeled Table A, presents results which were obtained from a one-month clinical trial. In this clinical trial, patients were topically administered either 1) a composition containing 0.2% brimonidine and 0.5% timolol twice a day (Combination), 2) a 0.5% timolol composition twice a day and a 0.2% brimonidine composition three times a day (Concurrent), or 3) a 0.2% brimonidine composition three times a day (Alphagan). The percentage of patients in the Combination group experiencing adverse events of the nervous system (0.0%) is lower than the percentage of patients experiencing adverse events of the nervous system in both

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.10
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as Express Mail (Label No. EL979880572US) in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on July 27, 2004.
Printed name of person making deposit: Adriane Giberson
Signature: Adriane Giberson Date: July 27, 2004

TIME OF PRESENTATION OF THE DECLARATION

This declaration is submitted prior to final rejection.

DECLARATION

4. As a person signing below:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on Information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

7. Expert in the Pharmaceutical Art

Full name expert: Rhett Schiffman, MD, MS, MHSA

Expert's signature: _____ Date: July 2, 2004
Country of Citizenship: USA
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TABLE A

All Adverse Events: Number (Percent) of Patients by Body System

(Safety Population)

Body System	Adverse Event (Preferred Term)	Combination (N=174)	Concurrent (N=167)	Alphagan (N=85)	P-value[a]
Digestive System	NAUSEA AND VOMITING	0 (0.0%)	0 (0.0%)	1 (1.2%)	0.200 [b]
Hemic and Lymphatic Syste	Overall	0 (0.0%)	0 (0.0%)	1 (1.2%)	0.200 [b]
	ANEMIA	0 (0.0%)	0 (0.0%)	1 (1.2%)	0.200 [b]
Metabolic and Nutritional Disorders	Overall	2 (1.1%)	1 (0.6%)	0 (0.0%)	>0.999 [b]
	PERIPHERAL EDEMA	1 (0.6%)	1 (0.6%)	0 (0.0%)	>0.999 [b]
	HYPERLIPEMIA	1 (0.6%)	0 (0.0%)	0 (0.0%)	>0.999 [b]
	HYPERGLYCEMIA	0 (0.0%)	1 (0.6%)	0 (0.0%)	0.592 [b]
Musculoskeletal System	Overall	1 (0.6%)	1 (0.6%)	1 (1.2%)	0.804 [b]
	ARTHRALGIA	1 (0.6%)	0 (0.0%)	0 (0.0%)	>0.999 [b]
	MYALGIA	0 (0.0%)	1 (0.6%)	0 (0.0%)	0.592 [b]
	TRAUMATIC BONE FRACTURE	0 (0.0%)	0 (0.0%)	1 (1.2%)	0.200 [b]
Nervous System	Overall	0 (0.0%)	5 (3.0%)	5 (5.9%)	0.003 [b]
	SOMNOLENCE	0 (0.0%)	2 (1.2%)	2 (2.4%)	0.113 [b]
	DEPRESSION	0 (0.0%)	2 (1.2%)	0 (0.0%)	0.193 [b]
	DIZZINESS	0 (0.0%)	1 (0.6%)	2 (2.4%)	0.054 [b]
	ATAXIA	0 (0.0%)	1 (0.6%)	0 (0.0%)	0.592 [b]
	INSOMNIA	0 (0.0%)	1 (0.6%)	0 (0.0%)	0.592 [b]
	INCOORDINATION	0 (0.0%)	0 (0.0%)	1 (1.2%)	0.200 [b]
Respiratory System	Overall	5 (2.9%)	6 (3.6%)	2 (2.4%)	0.850
	INFECTION SINUS	2 (1.1%)	0 (0.0%)	0 (0.0%)	0.679 [b]
	SINUSITIS	2 (1.1%)	0 (0.0%)	0 (0.0%)	0.679 [b]
	RHINITIS	1 (0.6%)	1 (0.6%)	0 (0.0%)	>0.999 [b]
	COUGH INCREASED	1 (0.6%)	0 (0.0%)	1 (1.2%)	0.513 [b]
	BRONCHITIS	0 (0.0%)	2 (1.2%)	0 (0.0%)	0.193 [b]

Note: All adverse events are represented, regardless of relationship to treatment.
Within each body system, preferred terms are sorted by descending frequencies of treatment groups from left to right.
Within each preferred term, a patient is counted at most once.

[a] A Pearson's chi-square test is performed to evaluate the equality of proportions among treatment groups unless otherwise noted.

[b] P-value is based on Fisher's exact test.